Statistical Analysis Plan

Study Title: Family psychoeducation for adults with psychotic disorders in Tanzania (NIMH R34, Baumgartner, PI, NCT04013932)

Document Date: June 21, 2021

Abbreviated Statistical Analysis Plan – Main Findings Analysis (Phase 3, Aim 4) to be submitted to clinicaltrials.gov

Family psychoeducation for adults with psychotic disorders in Tanzania (NIMH R34/Baumgartner, PI)

Overview

This study is a two-arm individually randomized group treatment (IRGT) trial. 66 patients will be enrolled and randomized with equal allocation into either treatment (n=33) or control (n=33) arms. Randomization is constrained on three variables thought to be strongly predictive of the primary outcome, WHOQOL score. These variables are study site, patient participant gender and patient participant years since illness onset. In addition, a relative of the patient (n=66) will be enrolled and followed for separate measured outcomes over the follow-up period (6 months). All treatment participants and their relatives will be assigned to one of six treatment groups. Control participants will receive usual care. All primary analyses will follow intention-to-treat (ITT) principles.

Study sites (2): Dar es Salaam; Mbeya

Participants: n=33 treatment participants; n=33 control participants; n=66 matched relatives (patient-relative dyads)

Group: The 33 treatment participants will be assigned to one of six groups (6 pp/6 groups)

Study time points: Baseline, Immediately post-intervention (~3 months), and ~6 months post-intervention

Primary endpoint: ~6 months post-intervention

Statistical Power

This pilot study was not powered to measure precise estimates of efficacy. However, a power calculation was performed to detect a difference in mean WHOQOL score at ~6-months post-intervention. Specifically, assuming we have 61 participants for analysis, representing a 5% loss to follow-up, we expect to have 80% power to be able to detect a mean difference of 1.8 or larger in the primary outcome, WHOQOL-BREF score, with a two-sided alpha level of 0.05 and a standard deviation of the mean difference of 2.5 or smaller.

Research Questions

Research Question 1: Does the change in the mean WHOQOL score differ between study arms, comparing baseline to ~6 months post-intervention?

Outcome: WHOQOL-BREF score

Effect measure: Difference-in-difference estimator of mean response, comparing endline (~6 months post-intervention) to baseline.

Research Question 2: Does the change in the mean WHODAS 2.0 score differ between study arms, comparing baseline to ~6 months post-intervention?

Outcome: WHODAS 2.0 score

Effect measure: Difference-in-difference estimator of mean response, comparing endline (~6 months post-intervention) to baseline.

Research Question 3: Does the change in the probability (risk) of **relapse** (hospitalized or non-hospitalized) differ between study arms at ~<u>6 months</u> post-intervention?

Outcome: relapse (hospitalized or non-hospitalized) immediately post-intervention to ~6-months post-intervention)

Effect measures: risk difference; risk ratio, rate ratio

Model specification:
A Similar modelling strategy will be used to answer each of the 3 primary research questions. Specifically, for research questions 1 and 2, we assume that the response variable is distributed Gaussian and a multivariate linear mixed model will be fitted to all three timepoints. Fixed effect parameters for study arm, timepoint (0,1,2) and their interaction will be fitted, as well as parameters for the design variables used in the constrained randomization process – study site, gender and years since illness onset (categorized as less than 4 years or greater than or equal to 4 years). Random effects will also be fitted to account for correlation in the response due to repeated measures within the same participant as well as measures for individuals within the same treatment group. A random slope for timepoint (0,1,2) will also be considered to account for variation in response trajectories over time. An unstructured covariance matrix will be assumed in modelling the random effects and restricted maximum likelihood estimation (REML) will be used for all estimation since the standard errors are known to be biased downward with ML. Interpretation will focus on the time-by-arm interaction parameter at ~6 months post-intervention, which will be interpreted as a difference-in-difference estimate of the effect of the intervention, comparing change in the mean response from baseline to ~6 months post-intervention, and whether this change differs by treatment arm, conditioning on covariates and random effects.

To handle missing response data at follow-up, we will consider both multiple imputation and inverse probability of censoring weighting techniques to account for any selection bias induced in the efficacy estimates.

To answer research question 3, we will utilize a similar multivariate mixed model approach, but because the response variable ('relapse') is binary, we will fit a generalized linear mixed model, assuming a Poisson response distribution and a log link. This 'modified Poisson' regression method with robust standard errors, will provide unbiased estimates of the risk ratio. Exponentiation of the time-by-arm interaction parameter at ~6 months post-intervention will be interpreted as the change in the relative risk of relapse during follow-up, and whether this change is different by treatment arm. A separate model fit with an identity link will provide an estimand of the risk difference for the time-by-arm interaction parameter. Both risk ratios and risk differences will be reported. In the event that median follow-up time is differential by treatment arm, we will employ a Poisson regression model with a log link and an offset term for the number of days eligible for the event. The model will include a parameter for treatment arm, as well as parameters for design variables, and exponentiation of the treatment parameter will be interpreted as a rate ratio, comparing the average rate of relapse in the treatment arm, compared to the control arm, conditional on covariates. Random effects will be handled similarly as for research questions 1 and 2.

All estimands will be reported with 95% confidence intervals. Hypothesis tests and p-values will be reported only for the three primary research questions and only for the ~6-months post-intervention contrast for each.